CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLORTHAL-DIMETHYL (DCPA)

Chemical Code # 000179, Tolerance # 00185
SB 950 # 031

May 8, 1987
Revised 12/6/88, 9/8/89, 1/07/91, 4/24/92, 10/1/92, 4/26/94

I. DATA GAP STATUS

Chronic/Oncogenicity, Rat:	No data gap, possible adverse effect
Chronic mouse:	No data gap, no adverse effects
Chronic dog:	No data gap, no adverse effect indicated[1]
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse reproductive effect[2]
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

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1 - See comment under heading "Chronic Dog". The study on file is not a guideline study but for reasons explained in the comment, no new study is being requested at this time.
2 - Adverse effects are chronic, not reproductive.
Note, Toxicology one-liners are attached
** indicates acceptable study
Bold face indicates possible adverse effect
File name: T940426
Revised by C. Aldous and J. Gee on 1/07/91; Silva, 4/24/92; Gee, 10/1/92, Kishiyama & Silva, 4/26/94.
Record numbers through 122143 and some record numbers over 900000 (through Document No. 185-059) have been examined.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

NOTE: This toxicology summary also contains studies performed with tetrachloroterephthalic acid (SDS-954), the diacid environmental metabolite of DCPA. These studies were provided due to groundwater contamination concerns. Studies found acceptable according to criteria applied to SB-950-mandated studies include rat teratology and one or more studies in each of the three general areas of mutagenicity tests. In addition, scientifically meaningful subchronic feeding (90-day) or gavage (30-day) studies have been performed. None of these studies indicated adverse effects except for a mouse micronucleus test (record 045:091598). That study identified a possible weak clastogenic effect at the highest dose only (10,000 mg/kg). That dose was twice the recommended maximum dose according to current guidelines ("TSCA Test Guidelines", Federal Register 52:(97), 5/20/87, 19080-19081), and was into the range which elicited bone marrow toxicity. For these reasons, this one "positive" finding does not indicate appreciable concern. It appears that a relatively high action level for groundwater would be supportable. Aldous, 1/7/91.

CHRONIC/ONCOGENICITY, RAT

**** 185 122143** "A Combined Chronic Toxicity/Oncogenicity Study in Rats with DCPA", (F. Lucas, M. Mizens and J. Laveglia, Ricera, Inc. Project ID 90-0005, 3/31/93. DCPA (Dacthal), purity of 97.7% (0.13% HCB was an impurity) was admixed with the feed at concentrations of 0, 1, 10, 50, 500 or 1000 mg/kg/day and fed to 10 and 60 Sprague-Dawley rats/sex/group for one and two years, respectively. NOEL = 1 mg/kg/day (Males showed an increased mortality at 1000 mg/kg. Clinical effects occurred primarily in males at $\geq$ 500 mg/kg: anogenital staining, animals appearing thin, material around nose or mouth (poor physical condition), few or no feces, soft feces, dark urine and urine red/red penile discharge (at 1000 mg/kg). Females

were thin at ≥ 500 mg/kg. Decreased body weight, body weight gain and food consumption were observed in females at ≥ 500 mg/kg and in males at 1000 mg/kg. Males showed decreased monocyte and T4 levels at ≥ 10 mg/kg and females showed decreased monocytes (≥ 500 mg/kg), decreased T4 (≥ 50 mg/kg) and increased cholesterol at ≥ 500 mg/kg. Liver weights were increased in both sexes at ≥ 500 mg/kg, kidney weights were increased in males at ≥ 50 mg/kg and in females at ≥ 500 mg/kg and thyroid/parathyroid weights were increased in males at 1000 mg/kg.) **Possible adverse effect:** Increased hepatocellular tumors at ≥ 500 mg/kg (females) and hepatocyte preneoplasia at ≥ 10 mg/kg (males), follicular cell adenomas at ≥ 50 mg/kg/day (males) and 1000 mg/kg (females). Retinal atrophy (females), lung lesions, thyroid nonneoplastic effects, hepatocytic hypertrophy, and chronic nephropathy were increased for dose levels at and above 10 mg/kg/day. ACCEPTABLE. (Kishiyama & Silva, 4/25/94).

Subchronic Study:

054 112030 "A 90-Day Feeding Study in Rats With Technical DCPA," (Lucas, F. and Benz, G., Ricerca, Inc., 1/22/91). DCPA technical (dimethyl-2,3,5,6-tetrachloroterephthalate, Lot #: 10148; 98.0% pure) was fed to CD VAF/Plus Sprague-Dawley rats (15/sex/dose) at 0, 50, 100, 150 and 1000 mg/kg for 90 days. In addition, 2 satellite groups at 0 and 1000 mg/kg (10 rats/sex/dose) were treated for 60 days and were used to examine lungs. NOEL = 50 mg/kg (Both sexes showed an increase in white foci in lung primarily at 1000 mg/kg. Liver and kidney showed a significant increase in weight primarily at ≥ 150 mg/kg. Epithelial hyperplasia, increased hyaline drops and infiltration in kidney were reported in males at ≥ 150 mg/kg. In both sexes, liver hypertrophy and accumulation of foamy macrophages in lung were reported at ≥ 100 mg/kg. In both sexes, clumped colloid and follicular hypertrophy were observed at 1000 mg/kg.) These data are supplemental (contains analysis of diet for study 011/036483). M. Silva, 1/28/92.

Chronic Study:

185-047 091841 Benz, G., Killeen, J.C., Lucas, F., Serrone, D.M.; "A chronic ophthalmology study in rats with technical DCPA". Ricerca, Inc., Dept. of Toxicology and Animal Metabolism,

Painesville OH (for in-life phase). Histopathology by EPL, Inc. Study completed Nov. 12, 1990. Rats (twenty/sex/group, VAF plus Crl:CD BR Sprague-Dawley) were dosed with 0, 2000/1000 ppm (dose reduced after week 22 until termination), or 20,000 ppm DCPA Technical for 2 years. Ophthalmological exams were performed 0, 3, 6, 12, 15, 18, and 24 months into the study. No treatment effects were noted in those exams, nor were there any treatment effects evident on histological examinations of eyes. Study is ACCEPTABLE to evaluate eye effects in rodents following chronic exposure to DCPA. (Aldous, 12/18/90).

[Subchronic effects studies on the diacid]

Subchronic Study:

NOTE: The available subchronic studies employing the diacid environmental breakdown product of chlorthal-dimethyl, 2,3,5,6-tetrachloroterephthalate, do not identify any adverse effects, as indicated in the one liners for two studies in Vol. 043, below. (Aldous, 1/7/91).

185-043 091587 "Ninety Day Toxicity Study in Rats", (IRDC, Jan 3, 1977).
DAC-1209, which is disodium 2,3,5,6-tetrachloroterephthalate, a white powder, purity not specified. Fed in the diet for 90 days at 0 (ground Purina Laboratory Chow), 50, 500, 1000, and 10000 (nominal) ppm to 15 Charles River CD rats/sex/group. High dose exposure may have been as low as 7500 ppm, based on assay of treated diet. The following observations were recorded: clinical symptoms, ophthalmoscopy, body weight, food consumption, hematology, serum chemistry, urinalysis, necropsy, and histopathology. No adverse effects indicated: (there were no definitive treatment effects). Apparent chronic NOEL $\geq$ 10000 ppm. NOT ACCEPTABLE, however acceptability is a moot issue (since the test article is not the a.i. and the study is ancillary by design). (H. Green, and C. Aldous, 1/7/91).

185-043 091588 Denice L. Major, B.A., "A 30-day oral intubation study in rats with tetrachloroterephthalic acid (SDS-954)", SDS Biotech Corporation, Painesville, OH., 2/1/85.
2,3,5,6-tetrachloroterephthalic acid, 99% purity, was administered by gavage for 30 days at 0

(0.5% (w/v) methylcellulose), 100, 500, and 2000 mg/kg/day to 10 CD (Sprague-Dawley) rats/sex/group. Soft stools were noted in both sexes at 2000 mg/kg/day. No adverse effects were indicated. NOEL = 500 mg/kg/day (soft stools at high dose). Supplemental information. (H. Green and C. Aldous, 1/2/91).

CHRONIC, DOG

The study in question, Record Number 036482 and supplement, 113498, has been addressed several times since 1985, when the initial review was conducted. The conclusion stated in the 4/21/92 review is valid but, given the interchanges between the registrant and DPR Medical Toxicology, the high doses used in the study in question and the lack of toxicity seen in the 1963 study at the high dose of 10,000 ppm, no further study in a non-rodent species is requested at this time. In reaching this conclusion, the total data base of long-term studies was considered. In 1988, US EPA considered the study to provide sufficient data on chronic effects. Gee, 10/1/92.

011, 055 036482, 113498 "Final Report: Two-Year Dietary Feeding - Dogs" and "A Homogeneity and 7-Day Stability Study of Dimethyl Tetrachloroterephthalate (DCPA, SDS-893) in Prepared Canine Diets," (Hazleton, L.W. & Dieterich, W.H., Hazleton Laboratories--chronic dog study, 11/15/63 & Walker, R.M. & Gruss, A.G., Ricerca, Inc.--retrospective diet analysis 2/28/92). Dacthal-T (Batch 4334-38, no purity stated) was fed to Beagle dogs (4/sex/group) at 0, 100, 1000 or 10000 ppm. An interim sacrifice was performed at 1 year (1/sex/group), at 2 years the remaining males and 2 females/group were terminated and at 26 months, 1 female/group was sacrificed. NOEL = 10000 ppm (No significant effects were observed in this study). The study was previously reviewed as unacceptable (A. Apostolou, 11/7/85 and Parker/Gee, 5/8/87--rebuttal). It was then re-reviewed as possibly upgradeable (Aldous, 12/18/90) upon receipt of the rat ophthalmology data. A retrospective diet analysis was then submitted (055 113498). Upon examination of all the data, it is concluded that there are too many major deficiencies that remain (Diet analysis was not performed in the original study. Histopathology was performed on "target organs" only in the mid and low dose animals. No histopathology on spinal cord, mammary gland or rectum. Animals were too old at initiation of dosing. Control animals were not healthy. No ophthalmology exam. An antihelmintic was administered twice during the study.). The study remains unacceptable and not upgradeable. M. Silva, 4/21/92.

EPA 1-liner: No core grade. Oncogenic NOEL > 10,000 ppm (HDT). [The June, 1988, Guidance for Reregistration indicates no further data are required for this category.]

ONCOGENICITY, RAT

011 036483 "Two-Year Dietary Administration - Rats," (Paynter, O.E., Hazleton Laboratories, Inc., 11/19/63). Dacthal-T (batch 4334-38, no purity stated) was fed in diet for 104 weeks to Charles River albino rats at 0, 100, 1000 or 10,000 ppm. There were 35/sex/dose (70/sex in control). However of the 35/sex/dose, 5/sex/dose were for interim sacrifices (10/sex in control)--performed at 13 & 52 weeks, which left only 25/sex/dose for the two-year feeding. NOEL $\geq$ 10,000 ppm (No toxicity was observed in this study.) Previously reviewed as unacceptable, but possibly upgradeable (A. Apostolou, 11/8/85), the status is now changed. After re-examining the data, it was observed that many, if not all of the animals were suffering from respiratory infection and were treated both i.m. and/or in drinking water with Chloromycetin palmitate, Combiotic, Terramycin and Tylocine throughout the study. Therefore, the effects of chlorthal-dimethyl, independent from the effects of the drugs used on the rats to treat for respiratory infection, could not be evaluated. The fact that the animals were sick is also sufficient reason to invalidate the study. Therefore, the study is now considered to be UNACCEPTABLE and not upgradeable. M. Silva, 1/29/92.
EPA 1-liner: No core grade. Oncogenic NOEL > 10,000 ppm (HDT)

ONCOGENICITY, MOUSE (Combined Study)

****185-031 071656** Powell, L.A.J., Coleman, M., Gopinath, C., Cherry, C.P., Gibson, W.A., and Crook, D.; "T-170-1: A combined chronic toxicity and tumorigenicity study in mice". [The above report by Huntingdon Research Centre Ltd. is included as "Appendix E" of a Ricerca Document (#1098-85-0057-TX-001). The Huntingdon Research Centre Ltd. Project I.D. is DSK 109/88383)]. The Huntingdon report was issued Sept. 9, 1988. The Ricerca report date was Oct. 6, 1988. Technical DCPA (T-170-1), purity 96.7%, was administered in the feed at concentrations of 0, 100, 1000, 3500, or 7500 ppm to 90 CD-1 mice/sex/group. Sixty mice/sex/group were designated for the 2-year lifetime study, whereas 10/sex/group were sacrificed at 27, 53, or 79 weeks. NOEL = 1000 ppm [slightly increased liver weights (both sexes)]. Microscopic changes were not increased in incidence below 7500 ppm and were minor in

degree at that dose, hence a conservative NOAEL is 3500. There was an increase in hepatocellular tumors in mice (statistically significant in females only) at 7500 ppm (a **possible adverse effect)**. Evidences of minimal liver toxicity at 7500 ppm included slightly increased incidence of "minimal centrilobular hepatocellular enlargement" in males and modest increases in SGPT and sorbitol dehydrogenase activities in females. Study is ACCEPTABLE as a combined study. (Kishiyama and Aldous, 12/14/90).

REPRODUCTION, RODENT

** 048 095905, "A Two Generation Reproduction Study in Rats with Technical DCPA", (F. Lucas, G. Benz and R. Lovell, Department of Toxicology and Animal Metabolism, Ricera, Inc., Project I.D. 88-0176, 12/21/90). Technical DCPA (purity 96-98%; Lot/Batch #: JK8401 & 10148) was administered in the feed at concentrations of 0, 1000, 5000, or 20,000 ppm/day to Sprague-Dawley CD VAF/Plus (35 rats/sex/group) for 2 generations (F0 & F1). The low and mid-doses were reduced to 200 and 500 ppm, respectively, on lactation day 0 of F2b litters. Chronic NOEL < 1000 ppm/day (Decreased body weight and body weight gain for both F0 & F1, both sexes at ≥ 5000 ppm was reported. Increased incidence of lung, kidney, thyroid and thymus lesions in both generations at all doses was observed histopathologically.) Reproduction NOEL = 5000 ppm (The mean stillborn index % was increased in all litters at 20000 ppm.) Pup NOEL = 1000 ppm (Decreased mean weight, day 1 in F1a & F1b at ≥ 5000 ppm and decreased mean live litter size, day 1 in F2a at 20000 ppm were reported.)
Treatment related chronic effects were found in the liver, lungs, kidneys, thymus and thyroid of F0 and F1 parental animals. No adverse reproductive effect. ACCEPTABLE. (Kishiyama & Silva, 11/21/91).

185-012 036484, "Reproduction Study - Albino Rats." (Hazleton Laboratories, 12/2/63). Dacthal-T, no purity stated; fed in the diet at 0, 1000 or 10,000 (1%) ppm, 8 males and 16 females mated per group; fed for 5 weeks before mating for two litters; reproductive NOEL = 1000 ppm (decreased pup weight gain); **possible adverse reproductive effect** with reduced fertility index and decreased pup weight gain at 10,000 ppm in the absence of overt parental

toxicity; UNACCEPTABLE (inadequate number of animals, insufficient length of pre-mating exposure, no histopathology, no necropsy of parental animals.) (A. Apostolou, 11/8/85).
EPA 1-liner: No core grade. Reproductive NOEL > 10,000 ppm (HDT)

185-047 091841 This volume discusses the reproduction study (048 095905) as concurrent with the special rat ophthalmology study, which has recently been reviewed). (Aldous, 12/18/90).

TERATOLOGY, RAT

** 185-015 050735, "A Teratology Study in Rats with Technical DCPA". (Document number: 712-5TX-85-0039-003 SDS-893). (Argus Research Laboratories, 5/29/86, Project No. 1019-002 where the Study Director was A. M. Hoberman, Ph.D.) Technical DCPA, 96.7%; Crl:COBS (SD) BR rats were given doses of 0, 500, 1000, 2000 mg/kg/day on days 6-15 of gestation, 25/group. No adverse effects. Maternal body weight gain decreased 20% on days 9-12 of gestation at 2000 mg/kg/day. Maternal NOEL = 1000 mg/kg/day (decreased weight gain), developmental NOEL > 2000 mg/kg/day. ACCEPTABLE. (D. Shimer and J. Gee, 5/6/87).

TERATOLOGY, RABBIT

** 185-034 074023 Schroeder, R.E., "A teratology study with T-171-1 in rabbits". [The above Bio/dynamics Inc. contract lab report is presented as "Appendix C" of a Ricerca, Inc. report having the same CDPR record number]. The Bio/dynamics Project I.D. No. is 87-3204, and the report is dated Nov. 7, 1988. The date of Ricerca report is 2/2/89. Technical DCPA, purity 95.5%, was administered by gavage at concentrations of 0 (0.5% methyl cellulose), 125, 250, and 500 mg/kg/day to 20 mated New Zealand White rabbits/group on days 7 through 19 of gestation. No adverse effect was indicated: there were no definitive maternal nor developmental effects in the dosage range tested in Bio/dynamics study No. 87-3204. When this Biodynamics study is considered along with the Argus teratology study in Appendix F of this

report (which has a separate CDPR review: see below), the composite maternal and developmental toxicity NOEL is 250 mg/kg/day (based on severe maternal toxicity, including mortalities, at 500 mg/kg/day; at that dose and above there were increased resorptions in does which died). ACCEPTABLE. Kishiyama and Aldous, 12/14/90.

185-034 074024, "A Pilot Teratology Study with Technical DCPA in Rabbits", (Bio/dynamics, Project I.D. Number 87-3203, 2/2/89). [Pilot to Bio/dynamics Project I.D. No. 87-3204; see 1-liner above for CDPR Record No. 074023, "Appendix C]. Technical DCPA, purity 95.5%, administered by gavage at 0 (0.5% methyl cellulose), 200, 500, 1000 or 2000 mg/kg/day to 6 mated New Zealand White rabbits/group for days 7 through 19 of gestation. Mortality (including moribund sacrifices, excluding one death due to an injury) was 0/6, 0/6, 1/5, 3/6, and 1/6 for controls through increasing dosage groups, respectively. Does which died generally suffered considerable weight loss before death. One surviving 2000 mg/kg/day dam also had great weight loss. Apparent maternal NOEL = 200 mg/kg/day (based on mortality). (Kishiyama and Aldous, 12/14/90).

185-034 (part 2 of 2) 074023 [presented by Ricerca report authors as Appendix F of an amalgamated report. That report also includes within it the complete Bio/Dynamics report of a teratology study (Project No. 87-3204) as Appendix C, and an Argus Laboratories range-finding study (Argus Project No. 1019-004P) as Appendix E]. Hoberman, A.M., "A teratology study in rabbits with T-170-1", Argus Research Laboratories, Inc., Horsham, PA, 9/25/87. DCPA, purity not stated, administered by gavage at concentrations of 0 (0.5% methylcellulose), 500, 1000 and 1500 mg/kg/day to 20 artificially inseminated New Zealand White rabbits/group on days 6 through 19 of gestation. Mortality (excluding intubation accidents) was 0/18, 4/20, 13/19, and 12/20 in controls through increasing dosage groups. Study is NOT ACCEPTABLE, and not upgradeable, due to paucity of pregnant does surviving to scheduled Caesarean sectioning (16, 13, 5, and 6 in controls through increasing dosage groups). The study was technically well-executed, and provides useful data. Clinical signs of toxicity associated with animals that died included: decreased motor activity, ataxia, impaired or lost righting reflex, moribundity, and dried or absent feces. Gastric ulceration was commonly observed in stomach

mucosae of does which died. There were often many resorptions in does which died: often total litters were resorbed. There was otherwise no indication of developmental toxicity. (Kishiyama and Aldous, 12/14/90).

185-012 036485, "Reproduction Study - Rabbits." [Evaluated as a teratology study] (Hazleton Laboratories, 6/2/64). Dacthal-T, batch no 4334-38, no purity stated; fed in the diet at 0, 1000 or 10,000 ppm (1%), days 8 through 16 of gestation, 6 New Zealand albino rabbits per group; 3 were sacrificed on 28th or 29th day of gestation and 3 gave birth; no adverse effect reported; UNACCEPTABLE (number of animals, no analysis of diets, no visceral or skeletal exam.) All doses were too low to establish a NOEL. (A. Apostolou, 11/8/85).
EPA 1-liner: No core grade. Reproductive NOEL > 10,000 ppm (HDT)

[Teratology study on the diacid]

**185-044 091590, "A teratology study in rats with tetrachloroterephthalic acid (SDS-954)". Elizabeth A. Lochry, Ph.D., Study Director, Argus Research Laboratories, Inc., Horsham, PA. Date of contract lab report, 8/28/85. The Argus report is incorporated into SDS Biotech Corp. Document # 687-5TX-84-0035-002. 2,3,5,6-tetrachloroterephthalic acid, 99% purity, was administered by gavage on gestation days 6 through 15 at 0 (0.5% (w/v) aqueous methylcellulose), 625, 1250, and 2500 mg/kg/day to 25 mated female Crl:COBS∗CD∗(SD)BR rats per group. Maternal NOEL = 625 mg/kg/day (excess salivation at 1250 and 2500 mg/kg/day). Increased incidences of excess salivation were noted at 1250 and 2500 mg/kg/day in 5 to 6 rats per group. Soft or liquid feces were observed in nearly all dams at 2500 mg/kg/day. Other less frequent signs at 2500 mg/kg/day included red or brown anal exudate, red colored mucus in feces, or redened anal region. Developmental NOEL $\geq$ 2500 mg/kg/day. No adverse effects were indicated. ACCEPTABLE. (H. Green and C. Aldous, 12/14/90).

185-043 091589 Range-finding study for Record #091590, above. Noted in that worksheet. No separate CDPR worksheet for this pilot study.

MUTAGENICITY, GENE MUTATION

** 027 068019, "L5178Y TK$^{+/-}$ Mouse Lymphoma Forward Mutation Assay with Technical Dimethyl Tetrachloroterephthalate (DCPA)", (Microbiological Associates, Inc., Rockville, MD, project T5554.701020 and Test Substance Analysis Laboratory, Ricerca, Inc., Painesville OH, Project I.D. 1488-87-0017, 4/15/88). Dimethyl tetrachloroterephthalate, purity 94.5%, tested at concentrations of 0 (acetone), 7.5, 10, 13, 18, 24, 32, 42, 56, 75 and 100 µg/ml without metabolic activation and 0, 15, 20, 27, 36, 47, 63, 84, 113, 150 and 200 µg/ml with rat liver activation in the first trial. Sporadic increases in mutation frequencies were observed without metabolic activation in both initial and confirmatory assays. However, a dose relationship was not observed and other criteria for a positive result were not met. Mutation frequency did not increase with metabolic activation in the initial or confirmatory assay. The results indicate DCPA (T-170-1) produced no response in both the presence and absence of exogeneous metabolic activation. ACCEPTABLE. (J. Kishiyama and J. Gee, 11/15/88).

** 027 067918, "Salmonella/Mammalian-Microsome Plate Mutagenicity Assay (Ames Test) with and without Metabolic Activation with Technical Dimethyl Tetrachloroterephthalate (DCPA)", (Microbiological Associates Inc., Project I.D. T5554.501014 and Test Substance Analysis Laboratory, Painesville OH, project I.D. 1488-87-0017, Document 1488-87-0029-TX-002, 4/14/88). Dimethyl tetrachloroterephthalate, 94.5% purity, at concentrations of 0 (acetone), 667, 1000, 3333, 6667 and 10000 µg/plate using Salmonella typhimurium strains TA98, TA100, TA15335, TA1537 and TA1538 (triplicate plates, two trials) was not mutagenic in the Ames Plate Incorporation Test with or without addition of rat liver metabolic activation system. Slight to moderate precipitation at all concentrations tested - no cytotoxicity. ACCEPTABLE. (J. Kishiyama and J. Gee, 11/15/88).

012 036486, "Activity of DTX-77-0003 in the Salmonella/Microsomal Assay for Bacterial Mutagenicity." (Microbiological Associates, 3/23/77, Report No. DS-002). DAC-893, Batch 1-32, 98%, 0.1% HCB (hexachlorobenzene); tested in strains TA1535, TA1537, TA1538, TA98 and TA100, with and without rat liver activation; triplicate plates, 0, 1, 10, 33.3, 100 or 333.3 ug/plate; high concentration based on a preliminary viability test with TA1538 in liquid culture following growth by OD_{560} for 24 hours. UNACCEPTABLE (no repeat trial, no individual plate counts but mean and standard deviation); no increase in reversion rate reported. (A. Apostolou, 11/8/85).
EPA 1-liner: Incomplete [no discussion]

[Gene Mutation studies on the diacid]

**185-044 091594, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with Tetrachloroterephthalic Acid", (Edmund G. Godek, Pharmakon Research International, Inc., Waverly, PA., Report # 666-5TX-84-0061-002, 10/26/84), 2, 3, 5, 6-tetrachloroterephthalic acid, 99% purity, reversion assay in triplicate plates in the presence and absence of activation (Aroclor 1254 induced Sprague Dawley rat liver fraction) with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 at 0 (95% ethanol), 50, 150, 500, and 1500 ug/plate. No increase in reversion frequency is indicated. ACCEPTABLE. (H. Green, 11/5/90 and Gee, 12/7/90)

**185-044 091595, "Mammalian Cell Forward Mutation Assay in the CHO/HGPRT System with Tetrachloroterephthalic Acid", (Edmund G. Godek, Pharmakon Research International, Inc., Waverly, PA., Report # 666-5TX-84-0072-002, 5/13/85), 2, 3, 5, 6-tetrachloroterephthalic acid, 99% purity, forward mutation assay (5-hour exposure) in duplicate cultures in the presence and absence of activation (Aroclor 1254 induced male Sprague-Dawley rat liver homogenate) with Chinese hamster ovary cells (clone K1, subclone BH4) at untreated, 0 (95% ethanol), 100, 500, 1000, 1500, and 2000 ug/ml. Seven-day expression time followed by mutant selection with thioguanine. No increase in forward mutation frequency. ACCEPTABLE. (H. Green, 11/7/90 and Gee, 12/7/90)

MUTAGENICITY, CHROMOSOME

**185-027 068020, "In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with DCPA", (Microbiological Associates Inc., Rockville MD, Study Number T5554.337002, 5/31/88). DCPA, purity 94.5%, was tested using Chinese Hamster ovary cells in absence and presence of an Arochlor-induced S-9 rat liver activation system at concentrations of 0 (acetone and untreated) 30, 100, 300 and 1000 µg/ml 4 hours treatment duplicate flasks harvested at 12 or 18 hours after initiation of treatment. DCPA did not increase chromosomal aberrations in CHO cells in metaphase with or without metabolic activation. ACCEPTABLE. (J. Kishiyama and J. Gee, 11/15/88).

**185-028 068022, " In Vitro Sister Chromatid Exchange (SCE) Assay in Chinese Hamster Ovary (CHO) Cells with Technical Dimethyl Tetrachloroterephthalate (DCPA)", (Microbiological Associates, Inc., Rockville MD., project I.D. T5554.334001 and Test Substance Analysis Laboratory, Painesville, OH, project I.D. 1488-87-0017, 5/19/88). DCPA, purity 94.5%, doses for the SCE assay were 0 (acetone), 38, 75, 150 and 300 µg/ml duplicate cultures, repeat trial: scored 50 metaphases per concentration and % in M_1 and M_2. Several statistically significant increases in SCEs/cell were observed; however, these increases were not reproducible nor dose dependent. DCPA was negative in the Chinese Hamster ovary sister

chromatid exchange assay with and without metabolic activation. ACCEPTABLE. (J. Kishiyama and J. Gee, 11/21/88).

185-012 036488, "Activity of DTX-77-0006 in the In Vivo Cytogenetic Assay in Rodents for Mutagenicity." (Microbiological Associates, 6/21/77, Project No. T1083). DAC-893, 98%, 0.1% HCB; given in a single dose to Sprague-Dawley rats, 5 males per group, tested at 0, 3.16, 31.6 or 316 mg/kg body weight; after 24 hours, animals were given colchicine i.p. and sacrificed after an additional 6 hours; scored a minimum of 50 mitotic figures per animal; no increase in aberrations at any dose; UNACCEPTABLE (use of only males without justification, single sacrifice time, route of administration not stated.)
(Shimer, 10/31/85 and A. Apostolou, 11/12/85).
EPA 1-liner: Inadequate.

185-012 036487, "Activity of DTX-77-0004 in the Dominant Lethal Assay in Rodents for Mutagenicity: Final Report." (Microbiological Associates, 7/1/77, Project No. T1077). DAC-893, 98%, 0.1% HCB; given in a single dose by oral gavage at 0, 3.16, 31.6 or 316 mg/kg/day to 10 males per group - dose selection based on a high dose of LD_5; mated with 2 females per male for 8 periods; reviewed as UNACCEPTABLE (inadequate number of pregnant females per group, inadequate high dose with no evidence of MTD) with a **possible adverse effect in post-implantation loss** at 31.6 (week 4) and 316 mg/kg (weeks 4 - 6), although the effect is weak. Report states that the values are within the range of historical controls but no data are presented. There were zero losses in the negative control and the low dose groups. A larger number of pregnant females would help resolve the significance of the effect. TEM was the positive control. (A. Apostolou, 11/12/85).
EPA 1-liner: Acceptable.

[Chromosomal effects studies on the diacid]

****185-045 091598**, "The Micronucleus Test in Mice with Tetrachloroterephthalic Acid (SDS-954)", (Dr. Gilbert Siou, Cytologie Experimentale et Recherche en Toxicologie Industrielle [C.E.R.T.I.], Laboratoire d'Histopathologie, 59, Avenue de Paris, Versailles, France, Report # 666-5TX-84-0071-002, 1/3/85), 2, 3, 5, 6-tetrachloroterephthalic acid, 99% purity, in vivo

bone marrow cytogenetics micronucleus assay with 7 Swiss mice/sex/group/sampling time. A single dose was administered by gavage; bone marrow was sampled 24, 48, and 72 hours later. Males were treated at 0 (Methocel E15 Premium (0.5% w/v)), 1000, 5000, and 10000 mg/kg. Females received 0, 500, 2500, and 5000 mg/kg. A preliminary test indicated females were more sensitive to the toxic effects than males. The polychromatic/normochromatic ratio of erythrocytes indicated that bone marrow toxicity occurred at 48 and 72 hours in males at the high dose and at 48 hours in females at the high dose. **An increase in the frequency of micronucleated polychromatic erythrocytes in males at the 48 hour sampling is indicated**.
ACCEPTABLE. (H. Green, 11/19/90 and Gee, 12/10/90)

MUTAGENICITY, DNA/OTHER

**185-028 068021, "Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with Technical Dimethyl Tetrachloroterephthalate (DCPA)", (Microbiological Associates Inc., Rockville, MD., Study number T5554.380009 and Test substance Analysis Laboratory, Painesville, OH, project I.D. 1488-87-0017, 5/19/88). DCPA, purity 94.5%, at concentrations of 0 (acetone), 3, 10, 30, 100, 300 and 1000 µg/ml was tested on primary rat hepatocytes. Initial and confirmatory assays reported no significant increase in the number of net nuclear grains; therefore, considered DCPA negative for inducing DNA damage/repair in cultured mammalian somatic cells. ACCEPTABLE. (J. Kishiyama and J. Gee, 11/21/88).

185-012 036489, "Activity of DTX-77-0005 in a Test for Differential Inhibition of Repair Deficient and Repair Competent Strains of S. typhimurium - The Repair Test." (Microbiological Associates, 3/23/77, Report No. DS-0001). DAC-893, 98%, 0.1% HCB; Salmonella strains TA1978 and TA1538; tested by adding compound to a disk at 0, 2, 10 or 20 ug/plate, in triplicate, with and without rat liver activation; no zones of inhibition reported. UNACCEPTABLE. Inadequate description of protocol, no individual plate values, positive control (chloramphenicol) did not appear to be effective. (J. Remsen (Gee), 11/12/85).
EPA 1-liner: Inadequate.

[DNA effects studies on the diacid]

**185-045 091596, "In Vitro Sister Chromatid Exchange Assay in Chinese Hamster Ovary Cells with Tetrachloroterephthalic Acid", (Juan R. SanSebastian, Ph.D., Pharmakon Research International, Inc., Waverly, PA., Report # 666-5TX-84-0062-002, 5/29/85), 2, 3, 5, 6-tetrachloroterephthalic acid, 99% purity, sister chromatid exchange assay (5 hour exposure) in the presence and absence of activation (Aroclor 1254 induced Sprague-Dawley rat liver fraction) in duplicate with Chinese Hamster ovary cells (CHO-K1-BH4) at untreated, 0(1.0% DMSO), 200, 500, 1000, 1500, and 2000 ug/ml. The pH of the test incubation medium was lowered to "acidic" upon addition of the ≥ 1000 µg/ml, limiting the highest practical concentration. No increase in the frequency of sister chromatid exchanges is indicated. ACCEPTABLE. (H. Green, 11/9/90 and J. Gee, 12/7/90).

**185-045 091597, "DNA Repair Test in Rat Hepatocyte Primary Cultures with Tetrachloroterephthalic Acid", (Thomas R. Barfknecht, Ph.D., Pharmakon Research International, Waverly, PA., Report # 666-5TX-84-0042-002, 11/30/84), 2, 3, 5, 6-tetrachloroterephthalic acid, 99% purity, tested in vitro unscheduled DNA synthesis assay in triplicate wells with male Fischer 344 rat hepatocytes at untreated, 0 (ethanol), 20, 60, 200, 600, 2000, and 6000 µg/well. Positive control was 2-AAF. No increase in unscheduled DNA synthesis id indicated. ACCEPTABLE. (H. Green, 11/16/90 and Gee, 12/10/90)

NEUROTOXICITY (Not required at this time)

003 941374 Non-validated IBT study in chickens.

METABOLISM

044 & 052 091591 & 093118 "Dacthal Animal Metabolism Studies," (Skinner, W.A. and Stallard, D.E., Diamond Alkali Company, 10/29/63). In vivo and in vitro tests were performed to determine the fate of DACTHAL herbicide and its metabolites (DAC-1449 = monomethyl tetrachloroterephthalate, DAC-954 = tetrachloroterephthalic acid).

Preliminary studies, using dogs (1/sex) from a DACTHAL 2-year chronic feeding study (0 and 10000 ppm groups) had urine and feces sampled during the 16th month. DACTHAL-T, used in the chronic study, contained 1.1% DAC-1449 and 1.7% DAC-954 as sodium salts. The results showed an excessive amount of DAC-1449 in the urine, which indicated the dogs were capable of hydrolyzing DACTHAL to DAC-1449 and possibly to DAC-954. Most of the DACTHAL was eliminated unchanged in the feces.

Tissues from the 2-year feeding study were analyzed for DACTHAL, DAC-1449 or DAC-954 in kidneys, liver, spleen and fat (3 males & 2 females at 10000 ppm). There was DAC-1449 and DAC-954 (no DACTHAL) in livers and kidneys, DAC-1449 in spleen (< 2 ppm) and < 1 ppm DACTHAL and < 2 ppm DAC-1449 was stored in fat (no DAC-954).

An in vitro study used DACTHAL in macerated beef liver samples (100 g/sample) at 5 ppm (final concentration). Samples were incubated at 390C, with agitation, then analyzed for DACTHAL, DAC-1449 and DAC-954 at 2, 4, 6, 21 and 29 hours. Results showed that liver enzymes could metabolize DACTHAL to DAC-1449, but only trace DAC-954 was formed after 29 hours.

The in vivo study used male mongrel dogs (3/group) treated with 100 or 1000 mg/kg "pure" DACTHAL or DAC-1209 (disodium salt of tetrachloroterephthalic acid--DAC-954) at 100 or 1000 mg DAC-954/kg body weight. At 1, 3, 6, 9, 12, 24, 48, 72 and 96 hours, blood, urine and feces were sampled for DACTHAL, DAC-1449 and DAC-954. **CONCLUSIONS:** DACTHAL can be hydrolyzed to the monomethyl ester of tetrachloroterephthalic acid (DAC-1449), then to tetrachloroterephthalic acid (DAC-954) in both the 2-year feeding study and the 1-dose metabolism study. According to the report, these metabolites are identical to those produced in soil and plants. No other metabolites have been identified. This report gave an acceptable, general summary of DACTHAL metabolism. Recovery, however, was very low in some instances and overly high in others. It was stated in the DAC-954 metabolism study that

because of the excessive amounts of the sodium salt occurring in the first feces sample, the conversion to DAC-954 for the purpose of analysis was incomplete and therefore, the total recovery of DAC-954 at 1000 mg/kg averaged only 37%. At 100 mg/kg, however, recovery was 123% (discounting dog #5871, for which the 24 hour feces sample was lost). The report also stated that contamination from feces in the DAC-954 metabolism study urine samples may account for the fact that there was a very sharp decline of DAC-954 at 12 hours, which subsequently declined at a slow rate. This explanation does not satisfactorily account for this occurrence, since the same phenomenon was reported for all at 1000 mg/kg and most at 100 mg/kg. NOTE: Study 044 091591 is an exact duplicate of 052 093188, except it also contains the following figures: Mean level of monomethyl ester of tetrachloroterephthalic acid in urine or blood of dogs administered pure DACTHAL; Mean level of tetrachloroterephthalic acid in dog urine or blood administered sodium salt of tetrachlorophthalic acid (4 figures). This volume was received 10/23/90 but was not reviewed at CDPR.
This report contains supplementary information. M. Silva, 12/3/91.

HUMAN DATA

052 093119 "Occupational Health Surveillance of Dacthal Workers." This was a memo from Morris Chelsky, MD, DrPH (August 3, 1987), commenting on the occupational health surveillance findings among workers engaged in Dacthal production, specifically whether eye effects have been observed from over-exposure from Dacthal. Dr. Chelsky was a medical epidemiologist for Diamond Shamrock Corporation (owner of the plant that produces Dacthal) and is currently a health surveillance consultant to Fermenta Plant Protection Company (current owner of Dacthal production plant). No cases of eye irritation have been reported and health surveillance findings of Dacthal workers has been satisfactory. No worksheet. M. Silva, 12/5/91. Toxicology one-liners are attached.